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Docket: 50821/15 PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY - US

EXPRESS MAIL LABEL NO.:	ER 620045532 US
Applicants:	NPS PHARMACEUTICALS, INC. IRINA SHCHERBAKOVA GUANGFEI HUANG OTTO GEOFFROY SATHEESH K. NAIR
Inventors:	IRINA SHCHERBAKOVA GUANGFEI HUANG OTTO GEOFFROY SATHEESH K. NAIR
International Application No.:	PCT/US04/10639
Title:	METHODS FOR PREPARING 2,3,5,6-SUBSTITUTED 3*H*-PYRIMIDIN-4-ONES
International Filing Date:	07 April 2004 (07.04.2004)
Priority Date:	07 April 2003 (07.04.2003)
Attorney Docket No.:	50821/15 PCT

AMENDMENT PURSUANT TO ARTICLE 34(2)(b) AND RULE 66.1, WITH ACCOMPANYING STATEMENT PURSUANT TO ARTICLE 19(1) AND RULE 46.4

MAIL STOP PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant respectfully submits this amendment and statement and requests reconsideration of the specification and claims as amended.

The application as filed includes Examples 1-8 and then skips to Examples 12-18. Examples 9-11 were inadvertently omitted at the time of filing this international application. However, Examples 9-11 were previously disclosed as Examples 12-14 in U.S. Provisional Application Serial No. 60/479,323 which was filed on June 18, 2003 and is titled Pyrimidinone Compounds as Calcilytics. Priority is claimed to Serial No. 60/479,323 and Serial No. 60/479,323 is incorporated by reference as indicated at paragraph 30 on page 9.

The specification as contained in the accompanying substitute pages 18-27 add Examples 9-11. The claims are contained on substitute pages 28-35 and are identical to the claims as originally filed. The abstract is contained on substitute page 36 and is identical to the abstract as originally filed.

DATED this 5TH day of November, 2004.

Respectfully submitted,

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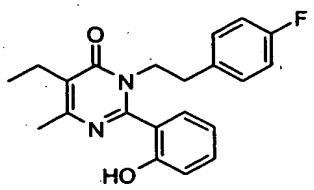
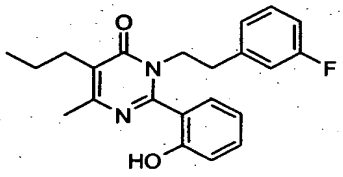


[0068] Utilizing the procedures described in Example 1a-g except substituting 2-ethyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 4-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 51% after crystallization from hexanes - ethyl acetate (5:1).

[0069] ^{1}H NMR ($CDCl_3$): δ 7.15 (dt, 1H, J_1 = 8.0, J_2 = 1.5), 7.06 (dd, 1H, J_1 = 7.8, J_2 = 1.5), 6.80 - 6.70 (m, 6H), 4.04 (t, 2H, J = 7.5), 2.78 (t, 2H, J = 7.5), 2.55 (q, 2H, J = 7.5), 2.24 (s, 3H), 1.10 (t, 3H, J = 7.5).

Example 9

Preparation of 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-5-propyl-3*H*-pyrimidin-4-one



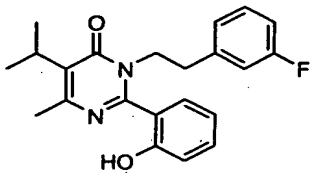
[0070] Utilizing the procedures described in Example 1a-g except substituting 2-propyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 12% after two crystallization from hexanes - ethyl acetate (10:1).

[0071] ^{1}H NMR ($CDCl_3$): δ 9.72 (broad s, 1H), 7.19 - 7.04 (m, 3H), 6.87 - 6.81 (m, 2H), 6.76 (d, 1H, J = 8.2), 6.63 (dd, 1H, J = 7.8), 6.50 (dt, 1H, J_1 = 8.2, J_2 = 1.8), 4.09 (t, 2H, J = 7.2), 2.82 (t, 2H, J = 7.2), 2.50 (t, 2H, J = 8.2), 2.25 (s, 3H), 1.53 (m, 2H), 0.98 (t, 3H, J = 7.2).

[0072] ^{13}C NMR ($CDCl_3$): δ 162.95 (d, J = 243), 162.67, 157.25, 156.04, 154.85, 140.28 (d, J = 7.2), 132.10, 130.15 (d, J = 8), 129.19, 124.57 (d, J = 2.4), 123.82, 120.65, 119.95, 117.73, 115.77 (d, J = 21), 113.72 (d, J = 21), 47.69, 34.16, 28.55, 21.60, 20.85, 14.48.

Example 10

Preparation of 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one



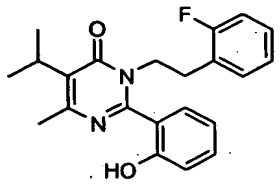
[0073] Utilizing the procedures described in Example 1a-g except substituting 2-isopropyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 52% after crystallization from hexanes - ethyl acetate (10:1).

[0074] ^1H NMR ($CDCl_3$): δ 7.21 - 7.09 (m, 3H), 6.85 (m, 2H), 6.76 (d, 1H, J = 8.1), 6.65 (d, 1H, J = 7.4), 6.52 (dd, 1H, J_1 = 8.1, J_2 = 1.5), 4.09 (t, 2H, J = 7.4), 3.10 (p, 1H, J = 7.0), 2.85 (t, 2H, J = 7.4), 2.27 (s, 3H), 1.35 (d, 6H, J = 7.0).

[0075] ^{13}C NMR ($CDCl_3$): δ 162.95 (d, J = 244), 161.70, 156.05, 155.19, 140.30 (d, J = 7), 132.15, 130.16 (d, J = 8), 128.98, 127.84, 124.57 (d, J = 2), 120.24, 119.85, 117.91, 115.78 (d, J = 21), 113.73 (d, J = 21), 47.47, 34.118, 28.24, 21.41, 19.68.

Example 11

Preparation of 3-[2-(2-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one



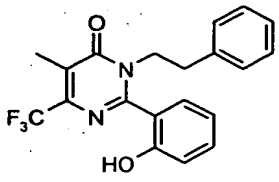
[0076] Utilizing the procedures described in Example 1a-g except substituting 2-isopropyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 2-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 50% after crystallization from hexanes - ethyl acetate (10:1).

[0077] ^{1}H NMR ($CDCl_3$): δ 10.10 (broad s, 1H), 7.20 - 7.10 (m, 2H), 7.04 (dd, 1H, J_1 = 7.7, J_2 = 1.6), 6.94 - 6.73 (m, 5H), 4.13 (t, 2H, J = 7.0), 3.10 (m, 1H), 2.94 (t, 2H, J = 7.0), 2.28 (s, 3H), 1.35 (d, 6H, J = 6.9).

[0078] ^{13}C NMR ($CDCl_3$): δ 161.81, 161.34 (d, J = 244), 156.14, 155.98, 158.26, 131.92, 131.34 (d, J = 4.5), 129.08, 128.65 (d, J = 7.8), 127.68, 124.76 (d, J = 16), 124.27 (d, J = 3.3), 120.00, 119.72, 117.46, 115.45 (d, J = 21.6), 46.31, 28.16, 27.85, 21.44, 19.67.

Example 12

Preparation of 2-(2-Hydroxy-phenyl)-5-methyl-3-phenethyl-6-trifluoromethyl-3*H*-pyrimidin-4-one



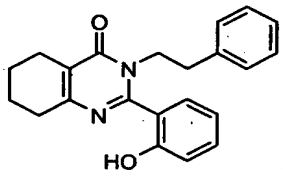
[0079] Utilizing the procedures described in Example 1a-g except substituting 2-trifluoromethyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a the title compound was prepared. Yield 20 % after three crystallizations from hexanes - ethyl acetate (2:1).

[0080] ^{1}H NMR ($CDCl_3$): δ 10.31 (s, 1H), 7.42 (m, 1H), 7.19 (m, 3H), 7.13 (dd, 1H, J_1 = 7.6, J_2 = 1.6), 7.01 (d, 1H, J = 7.9), 6.93 (m, 1H), 6.78 (m, 2H), 3.98 (t, 2H, J = 7.8), 2.79 (t, 2H, J = 7.8), 2.22 (q, 3H, J = 2.2).

[0081] ^{13}C NMR ($CDCl_3$): δ 162.05, 156.90, 153.88, 144.91 (q, J = 32), 137.61, 131.74, 129.66, 128.57, 128.33, 126.60, 122.40, 121.76 (q, J = 275), 121.40, 119.22, 115.76, 47.50, 33.17, 10.78.

Example 13

Preparation of 2-(2-Hydroxy-phenyl)-3-phenethyl-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one



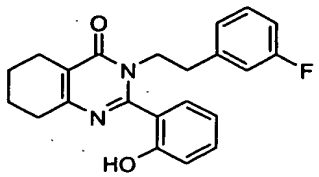
[0082] Utilizing the procedures described in Example 1a-g except substituting 2-oxo-cyclohexanecarboxylic acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a the title compound was prepared. Yield 55% after crystallization from hexanes - ethyl acetate (1:1).

[0083] ^{1}H NMR ($CDCl_3$): δ 10.00 (broad s, 1H), 7.14 - 7.00 (m, 5H), 6.80 – 6.69 (m, 4H), 4.02 (t, 2H, J = 7.4), 2.79 (t, 2H, J = 7.4), 2.5 (m, 4H), 1.68 (m, 4H).

[0084] ^{13}C NMR ($CDCl_3$): δ 162.42, 158.75, 156.29, 154.30, 137.87, 131.77, 129.36, 128.86, 128.59, 126.63, 121.33, 120.73, 119.85, 117.18, 47.60, 34.55, 30.79, 22.62, 21.97, 21.66.

Example 14

Preparation of 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one



[0085] Utilizing the procedures described in Example 1a-g except substituting 2-oxo-cyclohexanecarboxylic acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl

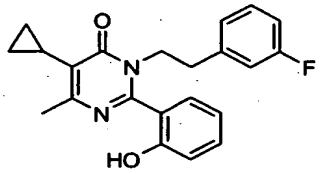
ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 56% after crystallization from hexanes - ethyl acetate (1:1).

[0086] ^{1}H NMR ($CDCl_3$): δ 10.10 (broad s, 1H), 7.15 - 7.02 (m, 3H), 6.78 – 6.81 (m, 2H), 6.70 (d, 1H, *J* = 8.1), 6.61 (d, 1H, *J* = 7.7), 6.46 (d, 1H, *J* = 8.1), 4.06 (t, 2H, *J* = 7.0), 2.79 (t, 2H, *J* = 7.0), 2.51 (m, 4H), 1.72 (m, 4H).

[0087] ^{13}C NMR ($CDCl_3$): δ 162.92 (d, *J* = 244), 162.42, 158.63, 156.27, 154.38, 140.30 (d, *J* = 7.3), 132.10, 130.14 (d, *J* = 8.3), 129.34, 124.57 (d, *J* = 2.2), 121.18, 120.85, 120.15, 118.02, 115.76 (d, *J* = 20.7), 113.70 (d, *J* = 21), 47.34, 34.25, 30.83, 22.68, 22.02, 21.71.

Example 15

Preparation of 5-Cyclopropyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one



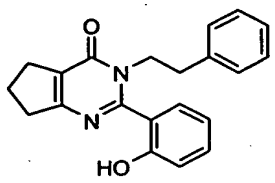
[0088] Utilizing the procedures described in Example 1a-g except substituting 2-cyclopropyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 56% after crystallization from hexanes - ethyl acetate (1:1).

[0089] ^{1}H NMR ($CDCl_3$): δ 9.70 (broad s, 1H), 7.31 (m, 1H), 7.15 (m, 2H), 6.91 (m, 3H), 6.70 (m, 1H), 6.59 (m, 1H), 4.25 (t, 2H, *J* = 7.6), 2.90 (t, 2H, *J* = 7.6), 2.38 (s, 3H), 1.61 (m, 1H), 0.99 (m, 2H), 0.87 (m, 2H).

[0090] ^{13}C NMR ($CDCl_3$): δ 162.77 (d, *J* = 245), 162.35, 159.27, 156.16, 154.91, 140.05 (d, *J* = 7.3), 132.10, 129.97 (d, *J* = 8.1), 128.83, 124.34 (d, *J* = 2.3), 122.95, 120.02, 119.82, 118.17, 115.55 (d, *J* = 21), 113.56 (d, *J* = 21), 47.40, 34.03, 21.22, 8.81, 6.64.

Example 16

Preparation of 2-(2-hydroxy-phenyl)-3-phenethyl-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one



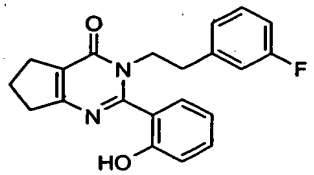
[0091] Utilizing the procedures described in Example 1a-g except substituting 2-oxo-cyclopentanecarboxylic acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a the title compound was prepared. Yield 52% after crystallization from hexanes - ethyl acetate (1:1).

[0092] ^{1}H NMR ($CDCl_3$): δ 9.12 (broad s, 1H), 7.17 (m, 5H), 6.85 (m, 4H), 4.18 (t, 2H, *J* = 7.8), 2.84 (m, 6H), 2.08 (m, 2H).

[0093] ^{13}C NMR ($CDCl_3$): δ 166.59, 160.72, 158.96, 154.47, 137.61, 131.87, 128.98, 128.70, 128.51, 126.58, 123.61, 120.88, 119.86, 117.75, 47.58, 34.57, 34.33, 27.83, 21.32.

Example 17

Preparation of 3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one



[0094] Utilizing the procedures described in Example 1a-g except substituting 2-oxo-cyclopentanecarboxylic acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 51% after crystallization from hexanes - ethyl acetate (1:1).

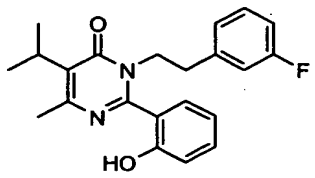
[0095] ^{1}H NMR ($CDCl_3$): δ 9.41 (broad s, 1H), 7.23 (m, 1H), 7.11 (m, 2H), 6.86 (m, 3H), 6.65 (d, 1H, *J* = 7.6), 6.51 (d, 1H, *J* = 9.6), 4.18 (t, 2H, *J* = 7.7), 2.84 (m, 6H), 2.09 (m, 2H).

[0096] ^{13}C NMR ($CDCl_3$): δ 166.95, 162.74 (d, *J* = 245), 160.64, 159.01, 154.20, 140.07 (d, *J* = 7.4), 131.88, 129.96 (d, *J* = 8.1), 128.99, 124.36, 123.61, 121.10,

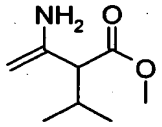
119.86, 117.40, 115.56 (d, J = 21), 113.53 (d, J = 21), 113.53 (d, J = 21), 47.14, 34.29, 34.19, 27.78, 21.29.

Example 18

Preparation of 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one

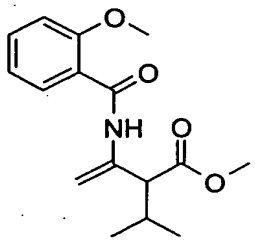


a). 3-Amino-2-isopropyl-but-3-enoic acid methyl ester.



[0097] 2-Methyl-3-oxo-butyric acid methyl ester (10 g, 0.0633 mol) was dissolved in absolute ethanol (50 mL). Excess of liquid ammonia (10 fold) was added and the mixture was stirred at room temperature in a sealed reaction vessel for 48 h. Excess ammonia and ethanol were removed under reduced pressure and the crude product (73% yield according to GC-MS data) was taken as such without further purification for the next synthetic step.

b). 2-Isopropyl-3-(2-methoxy-benzoylamino)-but-3-enoic acid methyl ester



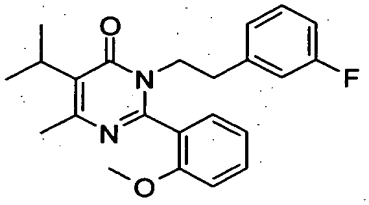
[0098] The crude 3-amino-2-isopropyl-but-3-enoic acid methyl ester of step 18a above in this method (5 g, 0.0318 mol) was dissolved in anhydrous THF (100 mL)

and anhydrous pyridine (5.2 mL, 0.0637 mol) was added. Anisoyl chloride (4.28 mL, 0.0318 mol) was added dropwise, and the mixture was refluxed for 2 hours. After cooling, water (100 mL) was added and the organic layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with 1N HCl (3 x 100 mL), water (100 mL), and brine (100 mL), dried over sodium sulfate and concentrated on a rotary evaporator. The product was purified by column chromatography over silica gel (200-400 mesh) eluting with 10% EtOAc/hexanes to give 2-isopropyl-3-(2-methoxy-benzoylamino)-but-3-enoic acid methyl ester (3 g, 33%) as a white powder.

[0099] ^{1}H NMR ($CDCl_3$): δ 0.93 (d, 3H, *J* = 6.6), 0.97 (d, 3H, *J* = 6.6), 2.10 - 2.23 (m, 1H), 2.73 (d, 1H, *J* = 11.1), 3.73 (s, 3H), 4.07 (s, 3H), 4.76 (d, 1H, *J* = 1.2), 6.09 (s, 1H), 7.00 (d, 1H, *J* = 8.1), 7.058 - 7.113 (m, 1H), 7.44 - 7.49 (m, 1H), 8.22 (dd, 1H, *J* = 1.8, 6), 9.96 (br s, 1H).

[00100] ^{13}C NMR ($CDCl_3$): δ 19.9, 21.0, 29.3, 51.9, 55.8, 60.7, 103.8, 111.4, 121.3, 121.8, 132.4, 133.0, 136.8, 157.4, 163.9, and 174.0.

c). 3-[2-(3-Fluoro-phenyl)-ethyl]-5-isopropyl-2-(2-methoxy-phenyl)-6-methyl-3H-pyrimidin-4-one

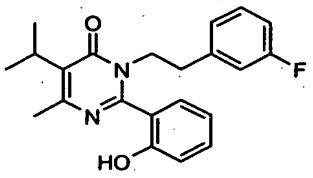


[00101] Phenyl magnesium bromide (1M solution in THF, 0.0021 mol) was added to a solution of 3-fluoro-phenethyl amine (0.27 mL, 0.0021 mol) in anhydrous toluene (20 mL). After stirring the mixture at 20°C for 10 min, 2-isopropyl-3-(2-methoxy-benzoylamino)-but-3-enoic acid methyl ester of step 18b above in this method (0.05 g, 0.0017 mol) was added. (Note that 2-isopropyl-3-(2-methoxy-benzoylamino)-but-3-enoic acid methyl ester or more generrically 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester provides another example of an appropriate carbamide for forming 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones once cyclized). The mixture was refluxed for 10 hours, cooled and ethyl acetate (50 mL) was added followed by 1N HCl (50 mL). The organic layer was separated and the aqueous layer was extracted

with EtOAc (3 x 50 mL). The combined organic extracts were washed with 1N HCl (3 x 100 mL), water (100 mL), and brine (100 mL). After drying over sodium sulfate and concentration on a rotary evaporator, the product was purified by column chromatography over silica gel (200-400 mesh) eluting with 12% EtOAc/hexanes to give 3-[2-(3-fluoro-phenyl)-ethyl]-5-isopropyl-2-(2-methoxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one (0.3 g, 46 %) as a white solid.

[00102] ^{1}H NMR δ 1.30 (d, 1H, *J* = 2.7), 1.31 (d, 1H, *J* = 2.7), 2.28 (s, 3H), 2.64 - 2.82 (m, 2H), 3.01 - 3.16 (m, 1H), 3.45 - 3.55 (m, 1H), 3.71 (s, 3H), 4.16 - 4.25 (m, 1H), 6.40 (td, 1H, *J* = 2.4, 9.6), 6.54 (d, 1H, *J* = 7.8), 6.87 - 7.08 (m, 4H), 7.35 - 7.41 (m, 1H).

d). 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one



[00103] A dry heavy-walled Pyrex tube was charged with 3-[2-(3-fluoro-phenyl)-ethyl]-5-isopropyl-2-(2-methoxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one of Example 18c (50 mg, 0.000132 mole), DMSO (5 mL) and sodium cyanide (65 mg, 10 equiv). The screw cap was tightened thoroughly. The reaction mixture was exposed to microwave irradiation at 180°C for 1 hour. The reaction mixture was allowed to reach room temperature and was carefully acidified with 50% HCl and extracted with ethyl acetate (3 x 25 mL). Caution, HCN may form. The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product, which was almost pure, was filtered through a short column packed with silica gel (200-400 mesh) using 25% EtOAc/hexanes to afford 35 mg (72%) of 3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one. ^{1}H and ^{13}C NMR spectral data of the compound were identical to those of the product prepared as described in Example 10.

[00104] It will be obvious to those having skill in the art that many changes may be made to the details of the above-described embodiments without departing from the underlying principles of the invention. The scope of the present invention should, therefore, be determined only by the following claims.

Claims

1. A method for preparing 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones comprising:

cyclizing an appropriate carbamide to obtain 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones.

2. The method as recited in claim 1, wherein the appropriate carbamide is an appropriate acetic acid 2-(1-alkyl-2-R^4-carbamoyl-alk-1-enylcarbamoyl)-phenyl ester.

3. The method as recited in claim 2, further comprising: acylation of an appropriate 3-amino-2-alkyl-alk-2-enoic acid R^4-amide to obtain the appropriate acetic acid 2-(1-alkyl-2-R^4-carbamoyl-alk-1-enylcarbamoyl)-phenyl ester.

4. The method as recited in claim 3, further comprising: reacting 2-alkyl-3-oxo-R^4-amide with anhydrous ammonia on catalysis by anhydrous aluminum chloride to obtain the appropriate 3-amino-2-alkyl-alk-2-enoic acid R^4-amide.

5. The method as recited in claim 4, further comprising: reacting 2-(2-alkyl-[1,3]dioxolan-2-yl)-*N*-R^4-alkanamide with *p*-toluenesulfonic acid monohydrate to obtain 2-alkyl-3-oxo-R^4-amide.

6. The method as recited in claim 5, further comprising: reacting 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid with oxalyl chloride followed by reaction with a primary amine to obtain 2-(2-alkyl-[1,3]dioxolan-2-yl)-*N*-R^4-alkanamide.

7. The method as recited in claim 6, further comprising: hydrolysis of 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid alkyl ester.

8. The method as recited in claim 7, further comprising: reacting of 2-alkyl-3-oxo-alkylic acid alkyl ester with ethylene glycol and *p*-toluenesulfonic acid monohydrate to obtain 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid alkyl ester.

9. The method as recited in claim 1, wherein the appropriate carbamide is an appropriate 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester.

10. The method as recited in claim 9, wherein the 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester is cyclized by reacting it with a primary amine and the Grignard reagent.

11. The method as recited in claim 9, wherein the 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester is obtained by acylation of an appropriate 3-amino-2-alkyl-but-3-enoic acid methyl ester.

12. The method as recited in claim 11, wherein the appropriate 3-amino-2-alkyl-but-3-enoic acid methyl ester is obtained by reacting 2-alkyl-3-oxo-butyric acid methyl ester with liquid ammonia.

13. The method as recited in claim 1, wherein the appropriate carbamide is 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester.

14. The method as recited in claim 13, wherein the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester is cyclized by reacting 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester with phenylmagnesium bromide and primary amine.

15. The method as recited in claim 13, wherein cyclizing the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester yields 2-(2-alkoxy-phenyl)-3-R^4-5,6-dialkyl-3*H*-pyrimidin-4-ones, and

wherein the method further comprises reacting 2-(2-alkoxy-phenyl)-3-R^4-5,6-dialkyl-3*H*-pyrimidin-4-ones with sodium cyanide under microwave irradiation to yield 3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one.

16. The method as recited in claim 13, wherein the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester is obtained by reacting 2-alkyl-3-oxo-butyric acid alkyl ester with liquid ammonia.

17. The method as recited in claim 1, wherein the 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones is at least one of:

2-(2-hydroxy-phenyl)-5,6-dimethyl-3-phenethyl-3*H*-pyrimidin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

5-ethyl-2-(2-hydroxy-phenyl)-6-methyl-3-phenethyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-5-propyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-methoxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-5-methyl-3-phenethyl-6-trifluoromethyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one;

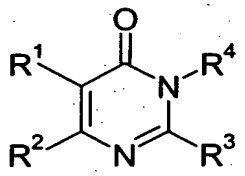
3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one;

5-cyclopropyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one; and

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one.

18. The method for preparing a compound having the chemical formula:



wherein:

R^1 and R^2 are either independently one of: H, halogen, CN, CF_3, lower alkyl, cycloalk, aryl; or R^1 and R^2 are together $-(CH_2)_n-$ and n is 5, 4, or 3;

R^3 is aryl group, which may have 1 to 4 substituents in the aryl ring each selected from the group consisting of: H, halogen, CN, CF_3, OCF_3, lower alkyl, N(lower alkyl)$_2$, lower alkoxy, OH, OC(O)-lower alkyl, OC(O)-lower alkylamino, and OC(O)-lower alkyl-N(lower alkyl)$_2$;

R^4 is H, lower alkyl, or a group of the formula $-(CH_2)_n-R^5$ wherein n is 0, 1, or 2, and

R^5 is an aryl group which may have 1 to 3 substituents on the aryl ring each selected from the group consisting of: H, halogen, CN, CF_3, OCF_3, lower alkyl, lower alkoxy, NH-lower alkyl, NH-alkylaryl, N(lower alkyl)$_2$, OH, OC(O)-lower alk, OC(O)-lower alkylamino, and OC(O)-lower alkyl-N(lower alk)$_2$;

and pharmaceutically acceptable salts or complexes;

comprising: cyclizing an appropriate carbamide to yield the compound.

19. The method as recited in claim 18, wherein the appropriate carbamide is an appropriate acetic acid 2-(1-alkyl-2-R^4-carbamoyl-alk-1-enylcarbamoyl)-phenyl ester.

20. The method as recited in claim 19, further comprising: acylation of an appropriate 3-amino-2-alkyl-alk-2-enoic acid R^4-amide to obtain the appropriate acetic acid 2-(1-alkyl-2-R^4-carbamoyl-alk-1-enylcarbamoyl)-phenyl ester.

21. The method as recited in claim 20, further comprising: reacting 2-alkyl-3-oxo-R^4-amide with anhydrous ammonia on catalysis by anhydrous aluminum chloride to obtain the appropriate 3-amino-2-alkyl-alk-2-enoic acid R^4-amide.

22. The method as recited in claim 21, further comprising: reacting 2-(2-alkyl-[1,3]dioxolan-2-yl)-*N*-R^4-alkanamide with *p*-toluenesulfonic acid monohydrate to obtain 2-alkyl-3-oxo-R^4-amide.

23. The method as recited in claim 22, further comprising: reacting 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid with oxalyl chloride followed by reaction with a primary amine to obtain 2-(2-alkyl-[1,3]dioxolan-2-yl)-*N*-R^4-alkanamide.

24. The method as recited in claim 23, further comprising: hydrolysis of 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid alkyl ester.

25. The method as recited in claim 24, further comprising: reacting of 2-alkyl-3-oxo-alkylic acid alkyl ester with ethylene glycol and *p*-toluenesulfonic acid monohydrate to obtain 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid alkyl ester.

26. The method as recited in claim 18, wherein the appropriate carbamide is an appropriate 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester.

27. The method as recited in claim 26, wherein the 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester is cyclized by reacting it with a primary amine and the Grignard reagent.

28. The method as recited in claim 26, wherein the 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester is obtained by acylation of an appropriate 3-amino-2-alkyl-but-3-enoic acid methyl ester.

29. The method as recited in claim 28, wherein the appropriate 3-amino-2-alkyl-but-3-enoic acid methyl ester is obtained by reacting 2-alkyl-3-oxo-butyric acid methyl ester with liquid ammonia.

30. The method as recited in claim 18, wherein the appropriate carbamide is 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester.

31. The method as recited in claim 30, wherein the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester is cyclized by reacting 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester with phenylmagnesium bromide and primary amine.

32. The method as recited in claim 30, wherein cyclizing the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester yields 2-(2-alkoxy-phenyl)-3-R^4-5,6-dialkyl-3*H*-pyrimidin-4-ones, and

wherein the method further comprises reacting 2-(2-alkoxy-phenyl)-3-R^4-5,6-dialkyl-3*H*-pyrimidin-4-ones with sodium cyanide under microwave irradiation to yield 3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one.

33. The method as recited in claim 30, wherein the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester is obtained by reacting 2-alkyl-3-oxo-butyric acid alkyl ester with liquid ammonia.

34. The method as recited in claim 18, wherein the 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones is at least one of:

2-(2-hydroxy-phenyl)-5,6-dimethyl-3-phenethyl-3*H*-pyrimidin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

5-ethyl-2-(2-hydroxy-phenyl)-6-methyl-3-phenethyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-5-propyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-methoxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-5-methyl-3-phenethyl-6-trifluoromethyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one;

5-cyclopropyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one; and

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one.

35. The method as recited in claim 18, wherein R^1 and R^2 are each lower alkyl.

36. The method as recited in claim 35, wherein said lower alkyl is one of methyl, ethyl, propyl, cyclopropyl and isopropyl.

37. The method as recited in claim 35, wherein R^2 is methyl.

38. The method as recited in claim 18, wherein R^1 and R^2 together are $-(CH_2)_n-$ and wherein n is 4 or 3.

39. The method as recited in claim 18, wherein R^1 and R^2 together are at least one of $-(CH_2)_4-$ and $-(CH_2)_3-$.

40. The method as recited in claim 18, wherein R^3 is phenyl optionally substituted with hydroxy.

41. The method as recited in claim 18, wherein
R^4 further comprises the group $-(CH_2)_n- R^5$;
wherein n is 1 or 2; and
R^5 is phenyl optionally substituted with 1 or 2 halogens.

42. The method as recited in claim 41, wherein n is 2 and said halogens are one of fluorine and chlorine.

Abstract of the Disclosure

Pyrimidinone compounds are disclosed. Methods of preparing the pyrimidinone compounds are also disclosed.